

## EAST Search History

| Ref # | Hits | Search Query          | DBs   | Default Operator | Plurals | Time Stamp       |
|-------|------|-----------------------|---|------------------|---------|------------------|
| L1    | 991  | merkulov.in.          | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR               | ON      | 2006/12/21 20:14 |
| L2    | 123  | L1 same gennady       | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR               | ON      | 2006/12/21 20:14 |
| L3    | 90   | L2 same V             | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR               | ON      | 2006/12/21 20:15 |
| L4    | 858  | Ketchum.in.           | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR               | ON      | 2006/12/21 20:15 |
| L5    | 292  | L4 same karen         | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR               | ON      | 2006/12/21 20:15 |
| L6    | 267  | L5 same A             | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR               | ON      | 2006/12/21 20:15 |
| L7    | 2812 | L4 (karen adj A)      | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR               | ON      | 2006/12/21 20:15 |
| L8    | 267  | L4 same (karen adj A) | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR               | ON      | 2006/12/21 20:16 |
| L9    | 248  | L8 and antibod\$      | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR               | ON      | 2006/12/21 20:16 |

## EAST Search History

|     |      |  |   |    |    |                  |
|-----|------|--|---|----|----|------------------|
| L10 | 856  | (Di adj Francesco).in.                 | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR | ON | 2006/12/21 20:17 |
| L11 | 531  | L10 same valentina                     | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR | ON | 2006/12/21 20:16 |
| L12 | 0    | (Valentina adj Di adj Francesco).in.   | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR | ON | 2006/12/21 20:17 |
| L13 | 0    | (Valentina adj (Di adj Francesco)).in. | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR | ON | 2006/12/21 20:17 |
| L14 | 2172 | Beasley.in.                            | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR | ON | 2006/12/21 20:17 |
| L15 | 606  | L14 same (ellen adj M)                 | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR | ON | 2006/12/21 20:18 |
| L16 | 548  | L15 and antibod\$                      | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR | ON | 2006/12/21 20:18 |
| L17 | 14   | L15 and lipase\$                       | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR | ON | 2006/12/21 20:18 |
| L18 | 7    | L9 and lipase                          | US-PGPUB;<br>USPAT;<br>USOCR;<br>EPO; JPO;<br>DERWENT;<br>IBM_TDB | OR | ON | 2006/12/21 20:18 |

FILE 'CAPLUS' ENTERED AT 20:19:27 ON 21 DEC 2006

E MERKULOV V GENNADY/AU 25

L1 20 S (E2)

E KETCHUM A KAREN/AU 25

L2 19 S (E49)

E DI FRANCESCO V/AU 25

L3 8 S (E3)

E BEASLEY ELLEN/AU 25

L4 8 S (E3)

<!--StartFragment-->RESULT 6

AAU98539

ID AAU98539 standard; protein; 427 AA.

XX

AC AAU98539;

XX

DT 21-AUG-2002 (first entry)

XX

DE Human lysosomal acid lipase protein #2.

XX

KW Human; lysosomal acid lipase; cancer; CNS; obesity; chromosome 10;  
KW central nervous system disorder; chronic obstructive pulmonary disease;  
KW diabetes; cardiovascular disorder; Alzheimer's disease; dementia;  
KW Parkinson's disease; multiple sclerosis; Huntington's disease; pain;  
KW congestive heart failure; myocardial infarction.

XX

OS Homo sapiens.

XX

PN WO200236754-A2.

XX

PD 10-MAY-2002.

XX

PF 26-OCT-2001; 2001WO-EP012382.

XX

PR 31-OCT-2000; 2000US-0244215P.

PR 06-DEC-2000; 2000US-0251401P.

XX

PA (FARB ) BAYER AG.

XX

PI Xiao Y;

XX

DR WPI; 2002-490007/52.

DR N-PSDB; ABK85978.

XX

PT Novel human lysosomal acid lipase polypeptide, useful for treating  
PT cancer, central nervous system disorder, obesity, chronic obstructive  
PT pulmonary disease, diabetes or cardiovascular disorder.

XX

PS Claim 1; Fig 5; 126pp; English.

XX

CC This invention relates to the DNA and protein sequences of a purified  
CC human lysosomal acid lipase protein. The sequences of the invention are  
CC useful for screening for agents which modulate the activity of human  
CC lysosomal acid lipase polypeptide. A compound which increases human  
CC lysosomal acid lipase activity may be identified as a potential  
CC therapeutic agent for increasing the activity of the human lysosomal acid  
CC lipase, and a test compound which decreases the human lysosomal acid  
CC lipase activity is identified as a potential therapeutic agent for  
CC decreasing the activity of human lysosomal acid lipase. A pharmaceutical  
CC compound containing the lysosomal acid lipase sequences is useful for the  
CC preparation of a medicament for modulating the activity of human  
CC lysosomal acid lipase in a disease such as cancer, central nervous system  
CC (CNS) disorder, obesity, chronic obstructive pulmonary disease, diabetes  
CC or a cardiovascular disorder. A reagent that modifies the activity of the  
CC protein of the invention is useful for treating a human lysosomal acid  
CC lipase dysfunction related disease, preferably the above mentioned  
CC diseases. A DNA or protein sequence of the invention is useful for  
CC treating the above mentioned disorders, where the CNS disorders are  
CC selected from Alzheimer's and Parkinson's disease, dementia, multiple  
CC sclerosis, Huntington's disease, and pain, and the cardiovascular  
CC disorder is selected from congestive heart failure and myocardial

CC infarction. The present sequence represents a human lysosomal acid lipase  
CC protein of the invention, the gene encoding this protein is located on  
CC human chromosome 10  
XX  
SQ Sequence 427 AA;

Query Match 95.0%; Score 2030; DB 5; Length 427;  
Best Local Similarity 97.2%; Pred. No. 2.3e-195;  
Matches 379; Conservative 2; Mismatches 7; Indels 2; Gaps 2;

```
Qy      1 MMWLLLTTCCLICGTLNAGGFLDLENEVNPEVWMNTSEIIYNGYPSEEEYVTTEDGYIL 60
      |||
Db      30 MMWLLLTTCCLICGTLNAGGFLDLENEVNPEVWMNTSEIIYNGYPSEEEYVTTEDGYIL 89

Qy      61 LVNRIPYGRTHARSTGPRPVVYMQHALFADNAYWLENYANGSLGFLLADAGYDVWMGNSR 120
      |||
Db      90 LVNRIPYGRTHARSTGPRPVVYMQHALFADNAYWLENYANGSLGFLLADAGYDVWMGNSR 149

Qy     121 GNTWSRRHKTLSSETDEKFWAFSFDDEMAKYDLPGVDFIVNKTGQEKLYFIGHSLGTTIGF 180
      |||
Db     150 GNTWSRRHKTLSSETDEKFWAFSFDDEMAKYDLPGVDFIVNKTGQEKLYFIGHSLGTTIGF 209

Qy     181 VAFSTMPELAQRIKMNFALGPTISFKYPTGIFTRFFLLPNSIIKAVFGTKGFFLEDKGTK 240
      |||
Db     210 VAFSTMPELAQRIKMNFALGPTISFKYPTGIFTRFFLLPNSIIKAVFGTKGFFLEDKGTK 269

Qy     241 IASTKICNNKILWLICSEFMSLWAGSNKKNMNQSRMDVYMSHAPTGSSVHNILHIKQLYH 300
      |||
Db     270 IASTKICNNKILWLICSEFMSLWAGSNKKNMNQSRMDVYMSHAPTGSSVHNILHIKQLYH 329

Qy     301 SDEFRAWDGNDADNMKHYNQSHPPYIDLTAMKVPTAIWAGGHDVLGTPQDVARILPQIK 360
      |||
Db     330 SDEFRAWDGNDADNMKHYNQSHPPYIDLTAMKVPTAIWAGGHDVLVTPQDVARILPQIK 389

Qy     361 SLSLVLSLLPEWEPTFDFVWGLDAPQRMFS 390
      |||
Db     390 SLH-YFKLLPDWN-HFDFVWGLDAPQRMYS 417
```

<!--EndFragment-->

<!--StartFragment-->RESULT 3

LICH\_HUMAN

103

ID LICH\_HUMAN STANDARD; PRT; 399 AA.  
AC P38571; Q16529; Q96EJ0;  
DT 01-OCT-1994, integrated into UniProtKB/Swiss-Prot.  
DT 21-JUN-2005, sequence version 2.  
DT 07-MAR-2006, entry version 55.  
DE Lysosomal acid lipase/cholesteryl ester hydrolase precursor  
DE (EC 3.1.1.13) (LAL) (Acid cholesteryl ester hydrolase) (Sterol  
DE esterase) (Lipase A) (Cholesteryl esterase).  
GN Name=LIPA;  
OS Homo sapiens (Human).  
OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;  
OC Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini; Hominidae;  
OC Homo.  
OX NCBI\_TaxID=9606;  
RN [1]  
RP NUCLEOTIDE SEQUENCE, PROTEIN SEQUENCE OF 196-212; 277-297 AND 305-315,  
RP AND VARIANT PRO-16.  
RX MEDLINE=92042192; PubMed=1718995;  
RA Anderson R.A., Sando G.N.;  
RT "Cloning and expression of cDNA encoding human lysosomal acid  
RT lipase/cholesteryl ester hydrolase. Similarities to gastric and  
RT lingual lipases.";  
RL J. Biol. Chem. 266:22479-22484(1991).  
RN [2]  
RP NUCLEOTIDE SEQUENCE.  
RC TISSUE=Liver;  
RX MEDLINE=94155897; PubMed=8112342;  
RA Ameis D., Merkel M., Eckerskorn C., Greten H.;  
RT "Purification, characterization and molecular cloning of human hepatic  
RT lysosomal acid lipase.";  
RL Eur. J. Biochem. 219:905-914(1994).  
RN [3]  
RP NUCLEOTIDE SEQUENCE.  
RC TISSUE=Liver;  
RX MEDLINE=96363957; PubMed=8725147;  
RA Du H., Witte D.P., Grabowski G.A.;  
RT "Tissue and cellular specific expression of murine lysosomal acid  
RT lipase mRNA and protein.";  
RL J. Lipid Res. 37:937-949(1996).  
RN [4]  
RP NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA], AND VARIANT PRO-16.  
RC TISSUE=Placenta;  
RX MEDLINE=22388257; PubMed=12477932; DOI=10.1073/pnas.242603899;  
RA Strausberg R.L., Feingold E.A., Grouse L.H., Derge J.G.,  
RA Klausner R.D., Collins F.S., Wagner L., Shenmen C.M., Schuler G.D.,  
RA Altschul S.F., Zeeberg B., Buetow K.H., Schaefer C.F., Bhat N.K.,  
RA Hopkins R.F., Jordan H., Moore T., Max S.I., Wang J., Hsieh F.,  
RA Diatchenko L., Marusina K., Farmer A.A., Rubin G.M., Hong L.,  
RA Stapleton M., Soares M.B., Bonaldo M.F., Casavant T.L., Scheetz T.E.,  
RA Brownstein M.J., Usdin T.B., Toshiyuki S., Carninci P., Prange C.,  
RA Raha S.S., Loquellano N.A., Peters G.J., Abramson R.D., Mullahy S.J.,  
RA Bosak S.A., McEwan P.J., McKernan K.J., Malek J.A., Gunaratne P.H.,  
RA Richards S., Worley K.C., Hale S., Garcia A.M., Gay L.J., Hulyk S.W.,  
RA Villalon D.K., Muzny D.M., Sodergren E.J., Lu X., Gibbs R.A.,  
RA Fahey J., Helton E., Kettelman M., Madan A., Rodrigues S., Sanchez A.,  
RA Whiting M., Madan A., Young A.C., Shevchenko Y., Bouffard G.G.,  
RA Blakesley R.W., Touchman J.W., Green E.D., Dickson M.C.,  
RA Rodriguez A.C., Grimwood J., Schmutz J., Myers R.M.,  
RA Butterfield Y.S.N., Krzywinski M.I., Skalska U., Smailus D.E.,

RA Schnerch A., Schein J.E., Jones S.J.M., Marra M.A.;  
 RT "Generation and initial analysis of more than 15,000 full-length human  
 RT and mouse cDNA sequences.";  
 RL Proc. Natl. Acad. Sci. U.S.A. 99:16899-16903(2002).  
 RN [5]  
 RP VARIANT CESD/WD PRO-200.  
 RX MEDLINE=94195814; PubMed=8146180;  
 RA Anderson R.A., Byrum R.S., Coates P.M., Sando G.N.;  
 RT "Mutations at the lysosomal acid cholesteryl ester hydrolase gene  
 RT locus in Wolman disease.";  
 RL Proc. Natl. Acad. Sci. U.S.A. 91:2718-2722(1994).  
 RN [6]  
 RP VARIANTS CESD ARG-129 AND PRO-129.  
 RX MEDLINE=98295576; PubMed=9633819;  
 RX DOI=10.1002/(SICI)1098-1004(1998)12:1<44::AID-HUMU7>3.3.CO;2-F;  
 RA Ries S., Buechler C., Schindler G., Aslanidis C., Ameis D., Gasche C.,  
 RA Jung N., Schambach A., Fehringer P., Vanier M.T., Belli D.C.,  
 RA Greten H., Schmitz G.;  
 RT "Different missense mutations in histidine-108 of lysosomal acid  
 RT lipase cause cholesteryl ester storage disease in unrelated compound  
 RT heterozygous and hemizygous individuals.";  
 RL Hum. Mutat. 12:44-51(1998).  
 CC -!- FUNCTION: Crucial for the intracellular hydrolysis of cholesteryl  
 CC esters and triglycerides that have been internalized via receptor-  
 CC mediated endocytosis of lipoprotein particles. Important in  
 CC mediating the effect of LDL (low density lipoprotein) uptake on  
 CC suppression of hydroxymethylglutaryl-CoA reductase and activation  
 CC of endogenous cellular cholesteryl ester formation.  
 CC -!- CATALYTIC ACTIVITY: A sterol ester + H(2)O = a sterol + a fatty  
 CC acid.  
 CC -!- SUBCELLULAR LOCATION: Lysosome.  
 CC -!- DISEASE: Defects in LIPA are the cause of Wolman disease (WD)  
 CC [MIM:278000]. WD is a severe manifestation of LIPA deficiency,  
 CC leading to the accumulation of cholesteryl esters and  
 CC triglycerides in most tissues of the body. WD occurs in infancy  
 CC and is nearly always fatal before the age of 1 year.  
 CC -!- DISEASE: Defects in LIPA are the cause of cholesteryl ester  
 CC storage disease (CESD) [MIM:278000]. CESD is a mild manifestation  
 CC of LIPA deficiency, leading to the accumulation of cholesteryl  
 CC esters and triglycerides in most tissues of the body. It is  
 CC characterized by late-onset.  
 CC -!- SIMILARITY: Belongs to the AB hydrolase superfamily. Lipase  
 CC family.  
 CC -----  
 CC Copyrighted by the UniProt Consortium, see <http://www.uniprot.org/terms>  
 CC Distributed under the Creative Commons Attribution-NoDerivs License  
 CC -----  
 DR EMBL; M74775; AAA59519.1; -; mRNA.  
 DR EMBL; U04285; AAB60327.1; -; Unassigned\_DNA.  
 DR EMBL; U04286; AAB60327.1; JOINED; Unassigned\_DNA.  
 DR EMBL; U04287; AAB60327.1; JOINED; Unassigned\_DNA.  
 DR EMBL; U04288; AAB60327.1; JOINED; Unassigned\_DNA.  
 DR EMBL; U04290; AAB60327.1; JOINED; Unassigned\_DNA.  
 DR EMBL; U04291; AAB60327.1; JOINED; Unassigned\_DNA.  
 DR EMBL; U04292; AAB60327.1; JOINED; Unassigned\_DNA.  
 DR EMBL; U04293; AAB60327.1; JOINED; Unassigned\_DNA.  
 DR EMBL; X76488; CAA54026.1; -; mRNA.  
 DR EMBL; Z31690; CAA83495.1; -; mRNA.  
 DR EMBL; U08464; AAB60328.1; -; mRNA.  
 DR EMBL; BC012287; AAH12287.1; -; mRNA.  
 DR PIR; S41408; S41408.

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DR      HSSP; P07098; 1HLG.
DR      Ensembl; ENSG00000107798; Homo sapiens.
DR      H-InvDB; HIX0009020; -.
DR      HGNC; HGNC:6617; LIPA.
DR      MIM; 278000; gene+phenotype.
DR      LinkHub; P38571; -.
DR      GO; GO:0005764; C:lysosome; TAS.
DR      GO; GO:0006487; P:protein amino acid N-linked glycosylation; TAS.
DR      InterPro; IPR006693; AB_hydro_lipase.
DR      InterPro; IPR000073; AB_hydrolase_1.
DR      InterPro; IPR008262; Lipase_AS.
DR      InterPro; IPR000379; Ser_estrs.
DR      Pfam; PF04083; Abhydro_lipase; 1.
DR      Pfam; PF00561; Abhydrolase_1; 1.
DR      PROSITE; PS00120; LIPASE_SER; 1.
KW      Direct protein sequencing; Disease mutation; Glycoprotein; Hydrolase;
KW      Lipid degradation; Lysosome; Polymorphism; Signal.
FT      SIGNAL          1      21      Potential.
FT      CHAIN           22     399     Lysosomal acid lipase/cholesteryl ester
FT                                     hydrolase.
FT                                     /FTId=PRO_0000017799.
FT      ACT_SITE        174     174     Charge relay system (By similarity).
FT      ACT_SITE        374     374     Charge relay system (By similarity).
FT      CARBOHYD         36      36      N-linked (GlcNAc . . .) (Potential).
FT      CARBOHYD         72      72      N-linked (GlcNAc . . .) (Potential).
FT      CARBOHYD        101     101     N-linked (GlcNAc . . .) (Potential).
FT      CARBOHYD        161     161     N-linked (GlcNAc . . .) (Potential).
FT      CARBOHYD        273     273     N-linked (GlcNAc . . .) (Potential).
FT      CARBOHYD        321     321     N-linked (GlcNAc . . .) (Potential).
FT      VARIANT          16      16      T -> P (in dbSNP:1051338).
FT                                     /FTId=VAR_004247.
FT      VARIANT         129     129     H -> P (in CESD).
FT                                     /FTId=VAR_004248.
FT      VARIANT         129     129     H -> R (in CESD).
FT                                     /FTId=VAR_004249.
FT      VARIANT         200     200     L -> P (in CESD and WD).
FT                                     /FTId=VAR_004250.
FT      CONFLICT         23      23      G -> R (in Ref. 3).
FT      CONFLICT         29      29      V -> L (in Ref. 4).
SQ      SEQUENCE       399 AA;  45419 MW;  AC75A7909DA9195A CRC64;

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|    |     |   |     |
|----|-----|---|-----|
| Qy | 2   | MWLLLT'TTCLICGTLNAGGF'LDLENEVNPEVWMNTSEIIINYGPSEEEYVTTEDGYILL             | 61  |
|    |     | :     :     :           :   |     |
| Db | 3   | MRFLGLVVCLVLWTLHSESGGKLTAVDPETNMNVSEIISYWGFPSSEYLVETEDGYILC               | 62  |
| Qy | 62  | VNRIPYGRTHARSTGPRPVVYMQHALFADNAYWLENYANGSLGFLLADAGYDVMWGNSRG              | 121 |
|    |     | :         :     :     :     :     :     :     :                           |     |
| Db | 63  | LNRIPHGRKNHSDKGPKPVVFLQHGLLADSSNWVTNLANSLSLGFILADAGF'DVMWGNSRG            | 122 |
| Qy | 122 | NTWSRRHKTLSETDEKFWAFSFDMAKYDLPGVIDFIVNKTGQEKLYFIGHSLGTTIGFV               | 181 |
|    |     | :         : :         :                 :     :         :     :         : |     |
| Db | 123 | NTWSRKHKTLVSQDEFWAFSYDEMAKYDLPASINFILNKTGQEQQVYVGHSSQGTIGFI               | 182 |
| Qy | 182 | AFSTMPELAQRIKMNFALGPTISFKYPTGIFTRFFLLPNSIIKAVFGTKGFFLEDKKTKI              | 241 |
|    |     | :                     :     :     :     :     :     :                     |     |
| Db | 183 | AFSIOPELAKRIKMFFALGPVASVAFCTSPMAKLGRLPDHLIKDLFGDKFEFLPOS AFLKW            | 242 |



Qy 242 ASTKICNNKILWLICSEFMSLWAGSNKKNMNQRSMDVYMSHAPTGSSVHNILHIKQLYHS 301  
| : | : | | : | | | : : | | : | | : : | | : | |  
Db 243 LGTHVCTHVILKELCGNLCFLLCGFNERNLNMSRVDVYTTHSPACTSVQNMLHWSQAVKF 302  
  
Qy 302 DEFRAVDWGNDADNMKHYNQSHPPYDLTAMKVPTAIWAGGHDVLGTPQDVARILPQIKS 361  
: : : : | | : | | | : : | | : : | | : : | | : | :  
Db 303 QKFQAFDWGSSAKNYFHYNQSYPPTYNVKDMLVPTAVWSGGHDWLADVDVNILLTQITN 362  
  
Qy 362 LSLVLSLLPEWEPTFDFVWGLDAPQRMFSGNHNL 395  
| : | | : | : | | | : : | : : | :  
Db 363 LVFHES-IPEWE-HLDFIWGLDAPWRLYNKIINL 394

<!--EndFragment-->